REMARKS

As described in the accompanying Request for Continued Examination, Applicants mistakenly filed a Response to Final Office Action under 37 C.F.R. §1.116 in the above-referenced application on 13 October 2010. This was incorrect as Applicants intended to file a Request for Continued Examination under 37 C.F.R. §1.114, which Request correctly includes a response to the 23 September 2009 Final Office Action. Accordingly, Applicants request that the Response to Final Office Action under 37 C.F.R. §1.116 mailed 13 October 2010 be replaced with the Request for Continued Examination under 37 C.F.R. §1.114 filed herewith. Applicants appreciate the guidance provided in Examiner Teller's return voice mail of 22 October 2010, describing how Applicants should proceed to correct this inadvertent error, and take steps to discount the incorrect submission under 37 C.F.R. §1.116 in favor of the complete and timely submitted Request for Continued Examination Under 37 C.F.R. §1.114 filed herewith.

I. Claim Status

Upon entry of this amendment, claims 43-58 are pending in this application. Claims 57 and 58 are new. No new matter is added by way of amendment as support for new claim 57 is found in at least claim 18 as originally filed. Support for claim 58 is found in at least paragraph [0152].

Entry of the amendments and new claims is respectfully requested.

II. Rejection of claims 43-56 under 35 U.S.C. §112, 1st paragraph

Claims 43-56 are rejected under 35 U.S.C. §112, 1st paragraph, for alleged lack of enablement. Specifically, while the Office Action admits that the recited method for treating diabetes is enabled for the eight exemplified heterocyclic carbonyl glycine compounds, it is alleged that the specification "does not reasonably provide enablement for a method for treating diabetes . . . comprising administering...an effective amount of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase...." (See Office Action, page 3.) Applicant respectfully traverses the rejection, especially in view of the concurrently filed Rule 132 declaration by inventor, Dr. Volkmar Guenzler-Pukall.

Applicant notes that the Office bears the burden of providing an explanation as to why the claims are not adequately enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). In the Advisory Action mailed 4 May 2010, the rejection of record is stated as standing for the reasons set forth in the previous Office Action. This earlier Office Action, mailed 23 September 2009, stated that "it is apparent that there is undue experimentation because of a variability in prediction of outcome that is not addressed by the present application. Absent factual data to the contrary, the amount and level of

experimentation needed is undue to practice the invention as claimed." (Office Action, pages 4 and 5.) It was further stated that "others skilled in the art would be unable to practice the invention as claimed without undue experimentation and with[out] a reasonable expectation of success, other than the use of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase, wherein the compound [is] selected from the group consisting of [eight exemplified compounds]." (Office Action, page 5.)

Applicant asserts that the Office has not met its burden as delineated by the court in *In re Marzocchi*, wherein the court held that the Office is required "to explain ***why*** it doubts the truth or accuracy of any statement in a supporting disclosure and ***to back up assertions of its own with acceptable evidence or reasoning*** which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis supplied)

Applicant respectfully submits that the enablement rejection is improper, because the Office neither explained why it doubts the truth or accuracy of the specification nor did it back up its assertions with acceptable evidence or reasoning. Instead, the Office merely alleges that "Applicant has provided no guidance of any other ingredient which act as a heterocyclic carbonyl glycine compound which inhibits a hypoxia inducible factor (HIF) hydroxylase." The Office does not present any factual findings demonstrating the unpredictability of heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase for their use in methods of treatment of diabetes or hyperglycemia. The mere assertion of lack of enablement is not sufficient for establishing a *prima facie* case of lack of enablement.

Contrary to the Office's assertions, the specification teaches that there are numerous heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase. Paragraph [0152] lists 10 issued patents, incorporated by reference, that disclose specific heterocyclic carbonyl glycine HIF hydroxylase inhibitor families. Please note that while these patents disclose prolyl-4-hydroxylase inhibitors, it was realized in the art, prior to the filing date of the instant application, that prolyl-4-hydroxylases are HIF hydroxylases and consequently, inhibitors of prolyl-4-hydroxylases also inhibit HIF hydroxylase. (See Ivan et al., (2001) Science 292:464-468; IDS mailed August 18, 2004) Therefore, Applicant asserts that numerous heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase were well known and readily available in the art.

Additionally, as attested to by Dr. Guenzler-Pukall, the **exemplified** heterocyclic carbonyl glycine compounds were drawn from these cited patents and are **representative** of the different heterocyclic carbonyl glycine HIF inhibitor families disclosed therein. More specifically, substituted quinoline-2-carboxamides, such as exemplified [(7-Chloro-3-hydroxy-quinoline-2-carbonyl)-amino]-acetic acid and [(3-Hydroxy-6-isopropoxy-quinoline-2-carbonyl)-amino]-acetic acid are disclosed in U.S. Patent Nos. 5,719,164 and 5,726,305. Substituted isoquinoline-3-carboxamides, such as exemplified [(1-Chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid, [(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, [(1-Chloro-4-hydroxy-7-methoxy-isoquinoline-3-carbonyl)-amino]-acetic acid and [(7-Benzyloxy-1-chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid methyl ester are disclosed in U.S. Patent No. 6,093,730. 3-hydroxypyridine carbonyl glycines, such as exemplified [(3-Hydroxy-pyridine-2-carbonyl)-amino]-acetic acid, are found in U.S. Patent Nos. 5,620,995 and 6,020,350. Applicant asserts that because of the incorporation by reference of the above heterocyclic carbonyl glycine families that include the exemplified compounds and their shared attributes with the other family members, the specification is enabled for methods of treatment of diabetes and hyperglycemia for at least these compound families.

Applicant further asserts that based on Dr. Guenzler-Pukall's declaration, the term "heterocyclic carboxyl glycine" is a term of art that would be recognized by a person of ordinary skill. Therefore, Applicant contends that a person of ordinary skill would readily be able to identify other compounds that meet this structural limitation and that could be assayed for HIF hydroxylase inhibitory activity.

Contrary to the Office's assertion, Applicant contends the specification offers adequate guidance for the identification of other heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase activity, because numerous assays for detecting such activity are disclosed. Paragraphs [0155]-[0160] and Example 14 detail assays that can be used to screen heterocyclic carbonyl compounds for HIF hydroxylase inhibitory activity. For example, in paragraph [0157] of the specification, the assay of Palmerini et al. is disclosed (Palmerini et al., J Chromatogr 339:285-292, 1985). This assay directly measures hydroxylated proline residues present on a target protein. It should be recalled that HIF-1α is constitutively expressed, but under normoxic conditions, HIF hydroxylase hydroxylates the proline residues in HIF-1α's oxygen-dependent degradation (ODD) domain allowing HIF-1α to be bound by the von Hippel Lindau tumor suppressor protein. The hydroxylated HIF-1α is then rapidly degraded in a proteosome-mediated pathway via a protein-ubiquitin ligase complex. Since the presence of proteins with hydroxylated proline residues in a sample indicate hydroxylase activity, compounds can be assayed for

their hydroxylase inhibitory activity by assaying for a reduction in hydroxylated prolines in the presence of a test compound compared to a control. This is an assay of Ivan et al. (Science 292:464-468, 2001; and Proc Natl Acad Sci USA 99:13459-13464, 2002) disclosed in paragraph [0158]. The specification further provides an exemplary HIF hydroxylase substrate, DLDLEMLAPYIPMDDDFQL (SEQ ID NO:5) that can be used in either of the described assays above.

An alternative way to measure HIF hydroxylase activity is based on the release of a reaction product. 2-oxoglutarate is a co-factor that is consumed by HIF hydroxylase producing succinate and CO_2 via decarboxylation of 2-oxoglutarate. The specification, in paragraph [0157], discloses two references that detail procedures for measuring succinate released from 2-oxoglutarate (Cunliffe et al. Biochem J 240:617-619, 1986; and Kaule and Gunzler, Anal Biochem 184:291-297, 1990). In paragraph [0160], the methodology of Hirsila et al. is disclosed regarding the assaying of CO_2 released by the decarboxylation of 2-oxoglutarate (Hirsila et al. J Biol Chem 278:30772-30780, 2003). Any compound that reduces or abolishes the rate of production of succinate or CO_2 in one of the above assays is a HIF hydroxylase inhibitor.

Since the product of the Von Hippel-Lindau (VHL) tumor suppressor gene, pVHL, binds to hydroxylated prolines in the ODD domain of HIF-α, a further method for assaying for HIF hydroxylase inhibitory activity measures the degree of binding between pVHL and HIF-1α or between pVHL and a peptide containing the ODD domain of HIF-1α in the presence or absence of a test compound. This method of Ivan et al. (Science 292:464-468, 2001; and Proc Natl Acad Sci USA 99:13459-13464, 2002) is disclosed in paragraph [0158]. Weak or absent binding is indicative that the test compound is a HIF hydroxylase inhibitor. International Publication No. WO 00/69908, also disclosed in paragraph [0158], is a similar assay.

As HIF-1α is rapidly degraded under normoxic conditions, a further method for assaying for a HIF hydroxylase inhibitors is to look for the presence of the HIF heterodimer, composed of HIF-1α and HIF-1β. This transcription factor normally forms only under hypoxic conditions, but is present under normoxic conditions when a HIF hydroxylase inhibitor is present. This assay is disclosed in Example 14.

As demonstrated above, there are numerous assays available to screen heterocyclic carbonyl glycine compounds for HIF hydroxylase inhibitory activity. As Dr. Guenzler-Pukall attests, to a person of skill the performance of such screening assays would be routine and does not represent undue experimentation. Therefore, equipped with knowledge of the assays, Applicant contends that a person of ordinary skill will

have a reasonable expectation of success in identifying other heterocyclic carbonyl glycine compounds that are useful in the recited methods without undue experimentation.

The Office further alleges that "it would not be predictable to the artisan which ingredient that inhibits HIF hydroxylase would work in the present invention, nor would it be predictable to the artisan which pathologies could be treated with these ingredients that act as a inhibitory substance." Applicant respectfully disagrees and notes that paragraph [0082] discloses that methods and compounds of the invention increase expression of genes whose products are involved in glucose uptake and utilization by cells including glucose transporter (GluT)-1, GluT-3, aldolase-A, enolase-1, hexokinase-1, hexokinase-2, phosphofructokinase-L, and phosphofructokinase-P. Applicant further notes that prior to the filing date of the instant application, it was well known in the art that numerous genes that express enzymes and other proteins involved in glucose uptake and utilization have HIF responsive elements. This statement is supported by the attached reference by Wenger that lists, in Table 1, 7 glucose metabolism genes that were known in 2000 to be regulated by HIF-1. (See Wenger, J. Exp. Biol,. 2000, attached as Exhibit B) Additionally, Applicant notes that Examples 2-4 provide methods for measuring the increase in expression of glucose transport and utilization genes.

According to Dr. Guenzler-Pukall, a person of ordinary skill would understand that the significance of inducing the expression of glucose transport and utilization genes with a HIF hydroxylase inhibitor as it relates to the lowering blood glucose levels. Further, a person of skill would realize the implications this would have in treating conditions that feature elevated blood glucose levels. Consequently, a person of skill would understand the usefulness of heterocyclic carbonyl glycine HIF hydroxylase inhibitors in treating pathologies, such as diabetes and hyperglycemia that feature elevated blood glucose levels.

Additionally, a person of skill could readily confirm the predicted decrease in blood glucose levels induced with treatment of heterocyclic carbonyl glycine HIF hydroxylase inhibitors through disclosed Examples 6-8. Here, the predicted lowering of blood glucose levels was observed using heterocyclic carbonyl glycine HIF hydroxylase inhibitors in both normal rats, Example 6, and in a mouse model of diabetes, Example 7. Long term lowering of blood glucose levels in diabetic mice using a heterocyclic carbonyl glycine HIF hydroxylase inhibitor was demonstrated in Example 8. Applicant contends that these experimental models and resultant data would provide a person of ordinary skill with a reasonable expectation of success in selecting other heterocyclic carbonyl glycine HIF hydroxylase inhibitors that can be used in the recited treatment methods.

In summary, the full scope of the recited claims are enabled as evidenced by the results achieved with the exemplified compounds, the relationship of the exemplified compounds to their family members, the disclosure of numerous assay systems for identifying further heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase and by the direct, causal relationship between the inhibition of HIF hydroxylase, the increase in expression of glucose transport and utilization genes and the reduction of blood glucose levels. Consequently, withdrawal of the rejection of claims 43-56 under 35 U.S.C. §112, 1st paragraph, is respectfully requested.

Applicant further asserts that limiting coverage to the specifically tested compounds goes against public policy as the court held in *In re Goffe*:

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)

In that case, the Office alleged that undue experimentation would be required to determine "suitable agglomerable materials," other than those specifically disclosed. The court found that the applicant provided 9 working examples and explained the manner in which the agglomerate layer worked, thus sufficiently enabling the scope of the claims sought.

Similarly, the Office has limited the scope of Applicant's claims to the 8 exemplified compounds while ignoring the disclosure of 10 patents that provide numerous other heterocyclic carbonyl glycine HIF hydroxylase inhibitors. These compounds are structurally related to the exemplified compounds and possess the same inhibitory activity. Therefore, claim 58, directed to these families of compounds is fully enable and should be allowed. Additionally, the Office has ignored the teachings of the application that explain the mechanism of action by which these compounds work and also ignored the disclosed assays that allow a person of skill to identify other heterocyclic carbonyl glycine compounds for use in the recited methods. Since a person of skill could readily and confidently identify other heterocyclic carbonyl glycines that inhibit HIF hydroxylase and can be used in the recited methods, claims 43-45 are fully enabled. Therefore, the full scope of the recited claims is enabled and claims 43-58 should be allowed. To do otherwise, is unjust and against public policy.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are fully in condition for allowance and request notification to that effect.

The Commissioner is hereby authorized to charge any fees necessary in this communication to Deposit Account No. 50-0811, referencing Docket No. FP0602.1 US.

Please call Applicant's representative at 415-978-1748 with any questions regarding this communication or the above-identified application.

Respectfully submitted,

Date: 22 October 2010

By: [signature] for

Paul Borchardt, Ph.D.
Reg. No. 53,999

Reg. No. 54,575

FibroGen, Inc.
409 Illinois Street
San Francisco, CA 94158
Main: 415-978-1200
Direct: 415-978-1748
Facsimile: 415-978-1917
pborchardt@fibrogen.com